REMARKS

A check for the fee for a two-month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 50-1213.

Claims 2-16, 18-27, 30, 32-34, 36, 37 and 40-45 are presently pending in this application. Claims 1, 17, 29, 31, 38 and 39 are cancelled without prejudice or disclaimer herein. Claims 38 and 39, which were withdrawn from consideration as being drawn to non-elected subject matter, are cancelled herein. Applicant reserves the right to file divisional applications to the non-elected subject matter.

Claims 2-16, 18-27, 30, 32-24, 36 and 37 are amended herein; claims 40-45 are added. Claims 32 and 36 are rewritten as independent claims incorporating the limitations of base claims.

Claims 2-22, 26, 27, 30, 33 and 34 are amended to depend on claim 32, which incorporates the limitations of claim 1. Claim 32 also is amended to render it clear that the vector to which the claim refers is a viral particle, not a nucleic acid molecule. Claims 40-45 are added to encompass subject matter that cancellation of claim 1 and amendment of claim 32 eliminated by virtue of the claim structure; and to include a claim to a kit containing the claimed combinations. Basis for a kit can be found in the specification, for example, at page 63, line 29 through page 64, line 5. Claims 8, 22, 23, 26, 27 30 and 34 also are amended to correct minor typographical errors and for grammatical clarity. Claim 23 also is amended to correct the name of the targeting agent which is abbreviated "SCF." Claim 23 previously identified this targeting agent as "serum cell factor;" the correct name for SCF is "stem cell factor." Basis for this amendment is found in the specification, for example, at page 9, lines 10-13, and at SEQ ID No. 10. Claims 24 and 25 are amended to include unabbreviated names for the listed abbreviations.

Claim 27 also is amended to replace "phosphorylate" with —to lead to—. The amendment finds basis, for example, on page 7, lines 10-14, of the specification. Claim 30 is amended to more clearly indicate the antecedent vector.

Claim 6 is amended in order to more particularly point out and distinctly claim the subject matter. Claim 3 provides the antecedent basis for "the linker." Hence, claim 6, which further describes the linker as a single amino acid or a peptide and is amended herein to depend on claim 3, now provides antecedent basis for "the linker."

Claims 13 and 14 are amended to more particularly point out that the recited bifunctional molecules contain antibody portions that are encoded by the recited nucleic acids. The amendments are supported by the specification, for example, at a page 8, line 28, through page 9, line 9.

Claim 2 is amended to indicate that the targeting agent is selected from proteins that bind to G-protein coupled receptors. Support for the amendment can be found in the specification, for example, at page 30, lines 5-10.

Claim 18 is amended to indicate that the antibody or portion specifically binds to penton base, penton fiber or the complex thereof. Support for the amendment can be found in the specification, for example, at page 20, lines 9-13.

Claim 37 is amended to indicate that the bifunctional molecule and delivery vector particle are complexed via penton in the vector particle. Support for this amendment can be found in the specification, for example, at page 31, lines 29-31.

No new matter has been introduced by the amendments.

Attention is directed to the publication of Wickham *et al.*, *J. Virology*, 70(10):6831-6838 (1996), which was cited in the Information Disclosure Statement delivered December 12, 2001.

THE REJECTION OF CLAIMS 6, 13 AND 14 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 6, 13 and 14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. The particular bases for the rejection are discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments and remarks herein.

Analysis

(1) Claim 6

The Office Action alleges that claim 6 is indefinite in the recitation of "the linker." Claim 6 is amended to depend from claim 3, which provides the antecedent basis for the linker, and thereby correcting this inadvertent error.

(2) Claims 13 and 14

The Office Action alleges that "the nucleic acid encoding an antibody portion" recited in claims 13 and 14 lacks antecedent basis, and further, that it is unclear whether these claims are directed to bifunctional molecules comprising an antibody protein or nucleic acid sequences encoding the antibody.

Claims 13 and 14 are amended to recite "a nucleic acid," thus, removing any recitation that might require antecedent basis for nucleic acid. In addition, as amended, claims 13 and 14 more particularly point out that the recited bifunctional molecules contain antibody portions encoded by nucleic acids. Thus, claims 13 and 14 are clearly directed to targeted delivery vector particles containing bifunctional molecules, where the antibody portions of the bifunctional molecules are further characterized as being encoded by the recited nucleic acids.

REJECTION OF CLAIMS 1-9, 12, 15-27, 29-34, 36 and 37 UNDER 35 U.S.C. §102(b)

Claims 1-9, 12, 15-27, 29-34, 36 and 37 are rejected under 35 U.S.C. §102(b) as being anticipated by Sosnowski *et al.* (WO 98/40508) because Sosnowski *et al.* discloses retargeted, tropism modified adenoviral vectors encoding a therapeutic gene, which are complexed with a molecule that contains

an antibody that binds to a component of the viral capsid and a targeting protein that binds to receptors capable of internalization on target cells. The Office Action further alleges that Sosnowski *et al.* discloses that the antibody that binds to the capsid can bind to the penton, which includes the penton base and penton fiber, and that examples of targeting proteins include FGF2, EGF, PDGF, VEGF and cytokines. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir. 1989), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter *is* identically disclosed or described in the "'prior art'" . . .the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a 103, obviousness rejection, where the applicant must be

afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkley, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA 1972).

CLAIMS

Claim 1 is cancelled herein.

Claim 32 is rewritten as an independent claim incorporating the subject matter of base claims 1 and 29. Claim 32 is directed to a targeted delivery vector particle that includes: a fiberless viral particle; a bifunctional molecule containing an antibody or antigen-binding portion and a targeting agent. The antibody or antigen-binding portion binds to an antigen in a protein that binds to α_v integrin, and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway; and the targeted delivery vector also includes a fiberless adenovirus vector.

Dependent claims 2-9, 12, 15, 16, 18-27, 30, 33-34 specify particulars of the targeted delivery vector particle of claim 32, such as targeting agents that trigger PI3K activation (claim 2); bifunctional molecules containing a linker (claims 3 and 6), a fusion protein (claim 4) or chemically conjugated polypeptides (claim 5); antibodies that contain a heavy chain (claim 7), Fab'2 fragment (claim 8), Fab fragment (claim 12), or a portion of the variable regions of heavy and light chains (claim 9); the type of protein that binds to α_v integrin (claim 16); the antibody or portion thereof specifically binds to the penton base of adenovirus (claim 18); the antibody or portion thereof specifically binds to an antigen that includes an RGD motif (claim 19); further details relating to the targeting agent (claims 15 and 20-25); the types of targeted cell surface proteins (claims 26 and 27); the product encoded by the delivery vector (claim 30); where the vector is a fiberless adenovirus vector (claim 32); where the bifunctional molecule and viral vector is

complexed (claim 33); and where the antibody portion of the bifunctional molecule is covalently linked to a viral particle surface protein (claim 34).

Claims 36 and 37 are directed to combinations of a fiberless adenoviral genome for delivering gene products to targeted cells; and a bifunctional molecule. The bifunctional molecules contains an antibody or antigen-binding portion and a targeting agent. The antibody or antigen-binding portion specifically binds to an antigen in a protein on a viral particle that binds to α_v integrin, and the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3K) signaling pathway.

Added claims 40, 41, 43 and 44 are directed to particles that include fiberless bacterial particles and bifunctional molecules that bind to a protein on the fiberless particle that binds to α_v integrin. Added claim 42 is outside the purview of this rejection. Thus, all of instant claims subject to this rejection or added herein require a fiberless particle as element.

Disclosure of Sosnowski *et al.*

Sosnowski *et al.* describes adenoviral vectors with modified tropism. Sosnowski *et al.* specifies that modified tropism can be accomplished by constructing an adenoviral vector presenting a ligand on its surface, or by conjugating a receptor-binding ligand with an antibody that binds to a viral protein (page 4, lines 17-25). The antibody-ligand conjugate can include an antibody that binds a viral capsid protein (see page 6, lines 25-26). Sosnowski *et al.* states that in various embodiments, the viral capsid protein is adenovirus fiber protein - for example, an adenovirus knob protein (page 8, line 30 to page 9, line 1). Sosnowski *et al.* further specifies that, to be useful in retargeting adenovirus, the recombinant fusion protein must bind to the adenovirus knob as well as the cognate receptor, and, adenovirus retargeting bifunctional fusion proteins are analyzed for their knob binding capacity (page 32, lines 19-21). The exemplary bifunctional fusion protein provided by Sosnowski *et al.* contains an anti-knob

protein antibody fragment conjugated to the FGF2 ligand (page 28, line 30, through page 29, line 2, and Examples beginning at page 97).

Sosnowski *et al.* does not disclose a targeted delivery vector particle that contains a bifunctional molecule and a fiberless adenovirus vector. Sosnowski *et al.* does not mention any fiberless particles nor elimination of fiber-encoding nucleic acid from the genome or from a particle.

Sosnowski *et al.* does not disclose a bifunctional fusion protein that contains an antibody or antigen-binding portion of an antibody that specifically binds to an adenoviral antigen that binds to α_v integrin. Nor does Sosnowski *et al.* disclose an antibody or portion thereof that specifically binds to the penton base of an adenovirus or that specifically binds to an antigen that includes an RGD motif. Sosnowski *et al.* appears to mention the penton only in the context of a description of the structure of the adenovirus (page 23, line 25, through page 24, line 10) or direct modification of the penton base to produce modified viral vectors (page 26, lines 5-7). Sosnowski *et al.* does not disclose a targeted delivery vector where the antibody portion of the bifunctional molecule is covalently linked to a viral or bacterial surface protein.

ANALYSIS

Sosnowski *et al.* does not disclose all of the elements of the claims

Sosnowski *et al.* does not anticipate any claims because Sosnowski *et al.* does not disclose vector genomes, vector particles or bifunctional molecules that include all elements as claimed in this application. Specifically, Sosnowski *et al.* does not disclose a fiberless adenovirus vector particle or a fiberless genome, nor an antibody that specifically binds an antigen in a protein that binds to α_v integrin.

Sosnowski *et al.* does not disclose a fiberless adenovirus particle or fiberless genome

Claim 32 is drawn to a targeted delivery vector particle that includes a fiberless adenovirus particle, a bifunctional molecule and a fiberless adenovirus vector genome. The remainder of the claims subject to this rejection depend on claim 32. Thus, all claims include a targeted delivery vector particle that includes a fiberless adenovirus particle, a bifunctional molecule and a fiberless adenovirus vector genome.

The Office Action does not point to a disclosure in Sosnowski *et al.* of a targeted delivery vector that includes a bifunctional molecule and a fiberless adenovirus vector. Moreover, no part of Sosnowski *et al.* discloses a targeted delivery vector that includes a bifunctional molecule and a fiberless adenovirus vector. Sosnowski discloses targeted vectors in which a ligand is attached to an adenovirus or discloses use of a bifunctional molecule that binds to the knob of adenovirus fiber (page 8, line 28, through page 9, line 1; page 28, line 23 through page 29, line 2). Sosnowski does not disclose fiberless particles or genomes that do not encode fiber (fiberless genomes).

Sosnowski *et al.* does not disclose an antibody that specifically binds an antigen in a protein that binds to α_v integrin

Sosnowski *et al.* does not disclose a bifunctional molecule that contains an antibody that specifically binds an antigen in a protein that binds to α_v integrin. The Office Action states that Sosnowski *et al.* discloses that the antibody that binds to the capsid can bind to the penton, which includes the penton base (which binds to α_v integrin) and penton fiber. For support of this statement, the Office Action points to pages 23-24 and 27 of Sosnowski *et al.* Pages 23-24 describe the structure of the penton and states that penton contains a fiber projection linked to the penton base, and further states that the adenovirus protein coat is composed of 252 subunits, 12 of which are pentons (page 23, line 25, through page 24, line 10). Pages 23-24 do not disclose an antibody that binds to the

penton, nor an antibody that specifically binds to an antigen in a protein that binds to α_v integrin. Page 27 discloses antibodies that neutralize or block a virus from targeting a cell using its native tropism, such as anti-knob antibodies (page 27, lines 17-19). Page 27 does not disclose an antibody that binds to the penton, nor an antibody that specifically binds to an antigen in a protein that binds to α_v integrin. Thus, none of pages 23-24 or 27 disclose an antibody that binds to the penton or an antibody that specifically binds to an antigen in a protein that binds to α_v integrin. Accordingly, the support relied on by the Office Action fails to disclose an antibody that binds to the penton, as alleged in the Office Action, or an antibody that specifically binds to an antigen in a protein that binds to α_v integrin, as recited in the claims. Therefore, the support relied on by the Office Action fails to disclose an element of the claimed targeted delivery vector particle.

In view of the fact that neither the portion of Sosnowski *et al.* relied on by the Office Action, nor any other portion of Sosnowski *et al.* discloses either (1) a targeted delivery vector particle including a bifunctional molecule and a fiberless adenovirus vector, or (2) an antibody that specifically binds to an antigen that binds to α_v integrin, Sosnowski *et al.* does not anticipate the targeted delivery vector particles of claim 32 or any claim dependent on claim 32 nor added claims 40-44.

REJECTION OF CLAIMS 1, 10, 11, 13 AND 14 UNDER 35 U.S.C. §103(a)

Claims 1, 10, 11, 13 and 14 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sosnowski *et al.* (WO 98/40508) in view of Stewart *et al.* (*EMBO J. 16(6)*:1189-1198 (1997)) because Sosnowski *et al.* teaches retargeted, tropism modified viral vectors, particularly adenoviral vectors encoding a therapeutic gene, which are complexed with a molecule that contains an antibody that binds to a component of the viral capsid and a targeting antibody that binds to receptors capable of internalization on target cells.

The Office Action further alleges Sosnowski *et al.* teaches that the antibody that binds to the capsid can bind to the penton, which includes the penton base

and penton fiber. The Office Action alleges that Stewart *et al.* teaches the DAV-1 antibody, which binds to the RGD sequence of the penton base of adenovirus.

The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the instant application was filed to use the anti-penton base-specific DAV-1 antibody, as allegedly taught by Stewart *et al.*, in the bifunctional molecules allegedly taught by Sosnowski *et al.*, to arrive at the instantly claimed subject matter.

It is respectfully submitted that this rejection is moot with respect to claims 10, 11, 13 and 14, which depend from claim 32, which was not subject to this rejection. This rejection is respectfully traversed insofar as it applies to claim 42.

Claim:

Claim 42 is directed to a bifunctional molecule, comprising:

an antibody or antigen-binding portion and a targeting agent, wherein:

the antibody or antigen-binding portion comprises all or a portion of DAV-1 antibody, wherein the portion thereof binds to a component of penton; and

the targeting agent specifically binds to a cell surface protein that activates the phosphatidylinositol 3 (PI3) signaling pathway.

RELEVANT LAW UNDER 35 U.S.C. §103

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior

art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Furthermore, the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from Merck [& Co. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also In re Deuel, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

To establish a *prima facie* case of obviousness in a genus-species situation, as in any other 35 U.S.C. §103 case, it is essential to find some motivation or suggestion to make the claimed invention in light of the prior art teachings. See, *e.g.*, In re Brouwer, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996); In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)); In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) ("[A] proper analysis under § 103 requires, inter alia, consideration of... whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process.").

Some motivation to select the claimed species or subgenus must be taught by the prior art. See, *e.g.*, Deuel, 51 F.3d at 1558-59, 34 USPQ2d at 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); Baird, 16 F.3d at 382-83, 29 USPQ2d at 1552; In re Bell, 991 F.2d 781, 784, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993) ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.").

Explicit findings on motivation or suggestion to select the claimed invention should also be articulated in order to support a 35 U.S.C. §103 ground of rejection. In re Dillon, 919 F.2d 688, 693, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990); In re Mills, 916 F.2d 680, 683, 16 USPQ2d 1430, 1433 (Fed. Cir. 1990). Conclusory statements of similarity or motivation, without any articulated rationale or evidentiary support, do not constitute sufficient factual findings.

Differences Between the Claims and the Teachings of the Cited References

Sosnowski *et al.* (WO 98/40508)

Sosnowski *et al.* is discussed above.

Stewart *et al.* (*EMBO J. 16(6)*:1189-1198 (1997))

Stewart *et al.* teaches the DAV-1 antibody, which binds a linear epitope of the adenovirus penton base protein (Abstract). Stewart *et al.* further teaches that binding of an Fab fragment of DAV-1 antibody to the RGD epitope of penton base blocks adenovirus infectivity (Abstract). Stewart *et al.* does not teach or suggest the use of bifunctional molecules.

ANALYSIS

It is respectfully submitted that the Office Action has not set forth a case of *prima facie* obviousness of the rejected claims because one ordinary skill in the art would not have been motivated to combine the teachings of Sosnowski *et al.* with the teachings of Stewart *et al.* to arrive at the claimed bifunctional molecules.

The cited references could not have motivated one of ordinary skill to arrive at the bifunctional molecules of claim 42.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination (In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). Sosnowski *et al.* does not teach or suggest a bifunctional molecule containing an antibody or antigen-binding portion thereof that specifically binds to a penton component. Sosnowski *et al.* teaches bifunctional molecules that contain antibodies that bind adenovirus knob protein. Sosnowski *et al.* states that these molecules can bind to adenovirus fiber, but Sosnowski *et al.* does not teach or suggest the desirability or use of binding to a penton component.

Stewart *et al.* does not teach or suggest any type of bifunctional molecule. Thus, the combination of the cited references, neither alone nor combined, teaches or suggest the desirability of combining selected disclosures of Sosnowski *et al.* and Stewart *et al.* to arrive at the bifunctional molecule containing an antibody or portion that specifically binds a penton component.

Hence the combination of Sosnowski *et al.* and Stewart relies on the improper use of the application at issue as a guide in combining references to yield the claimed product. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The teachings of Sosnowski *et al.* would not have motivated one of ordinary skill in the art to have used the antibody of Stewart *et al.*

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Sosnowski *et al.* teaches the importance of

preserving the virus' ability to internalize (page 28, lines 3-9), and that the penton base protein is important for adenoviral internalization (page 21, lines 12-14). In contrast, Stewart *et al.* teaches that the DAV-1 Fab inhibits adenoviral internalization by binding the penton base (Abstract). Thus, Stewart *et al.* teaches that the DAV-1 Fab inhibits internalization, while Sosnowski *et al.* teaches the importance of preserving internalization. Based on these teachings, the proposed modification of Sosnowski *et al.*'s bifunctional molecule with Stewart *et al.*'s antibody would to suggest that the resultant bifunctional molecule would inhibit internalization, thereby rendering the bifunctional molecule unsatisfactory for the purpose taught in Sosnowski *et al.*

Since the combined teachings would render the resultant bifunctional molecule unsatisfactory for Sosnowski *et al.*'s purpose, there is no suggestion or motivation to combine the cited references to make the proposed modification.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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